9:45 a.m.

883-6 **Acute Myocardial Infarction Study of Adenosine (AMISTAD II)**

Allan Ross, Ray Gibbons, Robert A. Kloner, Victor J. Marder, Gregg W. Stone, R Wayne Alexander, *George Washington University Medical Center, Washington, Dist. of Columbia, Emory University School of Medicine, Atlanta, Georgia.*

Background: A previous study of adenosine infusion in the treatment of acute myocardial infarction (AMISTAD I) suggested clinical efficacy. The potential role of adenosine as an effective therapeutic agent in the treatment of MI has remained in question. To approach this problem, a randomized, double blind, placebo controlled, multicenter trial (AMISTAD II) was performed.
Methods: The study involved 248 clinical sites in 13 countries (2,118 patients randomized) participating in the main trial, with 62 sites in 4 countries (263 patients) participating in a substudy utilizing Tc-99m sestamibi single photon emission computed tomography (SPECT) imaging at 120 to 216 hours post randomization for assessment of final infarct size.
Eligible patients with evolving anterolateral myocardial infarction were randomized to treatment with a 3 hour infusion of adenosine of 50 mcg/kg/min, 70 mcg/kg/min, or placebo. Patients received study medication within ±15 minutes of initiation of thrombolytic therapy or within 15 minutes prior to primary percutaneous mechanical reperfusion. Patients were followed until hospital discharge and throughout a 6 month period after randomization for assessment of primary and secondary endpoints, clinical events, and safety.
The primary efficacy endpoint was time from randomization to the first occurrence of congestive heart failure (CHF) in-hospital (>24 hours post randomization), or the first rehospitalization for CHF during follow-up, or death from any cause. The secondary efficacy endpoints were all cause mortality, cardiovascular mortality, and myocardial infarct size measured by SPECT imaging. Safety endpoints were assessed by following adverse events occurring during the first 48 hours following randomization, and changes in blood pressure and heart rate during the study drug infusion. Clinical events reported include all cause hospitalization, reinfarction, stroke, and revascularization (thrombolysis, percutaneous mechanical reperfusion, or coronary artery bypass graft surgery (CABG)).
Results: The enrollment and follow-up have been completed for all patients. Results will be available in fourth quarter 2001 and will be discussed.

ORAL CONTRIBUTIONS

886 Markers of Myocardial Ischemia

Wednesday, March 20, 2002, 10:30 a.m.-Noon
Georgia World Congress Center, Room 264W

10:30 a.m.

886-1 **Patients With Coronary Artery Disease Treated With Statins Have Decreased Heat Production From Culprit Lesions**

Christodoulos Stefanadis, Konstantinos Toutouzas, Eleftherios Tsiamis, Manolis Vavouranakis, Ioannis Kallikazaros, Sophia Vaina, Christina Chrysochoou, Dimos Panagiotakos, Christos Pitsavos, Pavlos Toutouzas, *Hippokration Hospital, Athens, Greece.*

Background: It has been previously shown, that a local inflammatory process is involved in atherosclerotic plaques, resulting in increased heat production of the culprit lesions. Also, it has been shown that statins may play an important role in plaque stabilization, due to an additional anti-inflammatory effect. The purpose of the present study was to evaluate the effect of statins on atherosclerotic plaque stabilization by measuring the temperature of atherosclerotic plaques. **Methods:** The study population included 86 patients (pts), 26 pts with stable angina (SA), 36 pts with unstable angina (UA), and 24 pts with acute myocardial infarction (AMI). All pts underwent diagnostic catheterization. Under statin treatment were 46 pts (14 pts with SA, 18 pts with UA and 14 pts with AMI) for a period of over a month, and 40 pts were not receiving statins (12 pts with SA, 18 pts with UA and 10 pts with AMI). Aspirin was administered in 65 pts. Total cholesterol and low-density cholesterol were measured in all pts. During the diagnostic catheterization, we measured the temperature difference (TD) between the atherosclerotic plaque and the healthy vessel wall with a thermography catheter previously validated (Medispes S.W.A.G.zug-Switzerland). **Results:** TD was progressively increased form pts with SA to UA and AMI (0.32 ± 0.1 vs 0.41 ± 0.28 vs 0.68 ± 0.41°C, $p < 0.02$). When we categorized the study population into pts receiving statins and pts not treated with statins, TD was lower in the treated group (0.30 ± 0.31 vs 0.57 ± 0.40°C, $p < 0.01$). Moreover, treated pts within each clinical syndrome had lower TD compared to untreated pts (SA: 0.23 ± 0.16 vs. 0.42 ± 0.24°C, $p < 0.02$, UA: 0.29 ± 0.25 vs. 0.45 ± 0.26°C, $p < 0.02$ and AMI: 0.56 ± 0.34 vs. 0.82 ± 0.51°C, $p < 0.01$). Multivariate analysis showed that treatment with statins was an independent factor in the assessment of temperature variation, adjusted for age, hypercholesterolemia, hypertension, smoking, aspirin intake, and clinical syndrome. **Conclusions:** Treatment with statins results in less heat production from the culprit lesion, indicating stabilization of the culprit atherosclerotic plaque.

10:45 a.m.

886-2 **Excessive Tumour Necrosis Factor Activation Post-Infarction Contributes to the Early Susceptibility to Myocardial Rupture: Evidence From TNF-/- Transgenic Knockout Models**

Mei Sun, Fayez Dawood, Wen-Hu Wen, Josef Penninger, Peter Liu, *Heart & Stroke/ Richard Lewar Centre of Excellence, U of Toronto, Toronto, Ontario, Canada, Toronto General Hospital, UHN, Toronto, Ontario, Canada.*

BACKGROUND: We have previously demonstrated that tumour necrosis factor (TNF) is expressed in high levels in the post-infarction (MI) myocardium, and may orchestrate inflammation and matrix repair. However, excessive TNF activation may contribute to early myocardial rupture.
METHODS: To examine the role of TNF levels in matrix healing post MI, we generated MI in C57/BL wild type mice that are rupture prone, and compared them to TNF-/- homozygous knockout animals in the same background. The animals were randomized to LAD ligation or sham operation, and the mortality, ventricular morphology, inflammatory cell infiltrate and local collagen formation were compared.
RESULTS: The wild type C57BL mice had higher of mortality post MI at 21 days (67% in TNF+/+ and 43% in TNF-/-, $p<0.05$), with the early deaths between days 3-7 were mainly attributed to myocardial rupture. Pathology revealed extensive inflammatory cell infiltrate and poor collagen formation in the wild type animals, associated with very high levels of local TNF production. Knockout TNF-/- littermates in contrast had lower incidence of rupture, and more attenuated inflammatory infiltrate, but more late ventricular dilatation in the survivors. Apoptosis detected by TUNEL and DNA ligase techniques showed extensive signals in the infarct, border as well as normal remote zone in wild type animals, but significantly attenuated in the TNF-/- models. MMP9 activation, associated with wound repair, was extensive in the TNF-/- mice, but was confined only to the central infarct zone in the wild type animals prone to rupture.
CONCLUSIONS: We conclude that host predisposition towards high TNF production in the post MI myocardium lends susceptibility to infarct rupture. The ability to decrease excessive TNF production leads to improved scar formation, less myocardial rupture and lower mortality, and may represent an interesting approach in high risk rupture prone situations post-myocardial infarction.

11:00 a.m.

886-3 **Sphingosine Contributes to Tumor Necrosis Factor-a-Mediated Contractile Dysfunction in Response to Coronary Microembolization**

Matthias Thielmann, Claus Martin, Hilmar Dörge, Sergej Belosjorow, Uwe Schwanke, Arne Krüger, Anita van de Sand, Ina Konietzka, Rainer Schulz, Gerd Heusch, *Department of Pathophysiology, University of Essen, Essen, Germany.*

Backround: Coronary microembolization results in patchy microinfarction, leukocyte infiltration, and increased myocardial tumor necrosis factor-α (TNF-α) levels and finally progressive myocardial contractile dysfunction. The negative inotropic effects of TNF-α in vitro are in part mediated by sphingosine. We therefore examined the effect of the ceramidase inhibitor N-oleoylethanolamine (NOE) on myocardial TNF-α content (WEHI cytolytic cell assay), sphingosine content (HPLC) and contractile function (sonomicrometry) after coronary microembolization in vivo.
Methods: In enflurane-anesthetized dogs, coronary microembolization was induced by infusion of 3,000 microspheres (42 µm diameter) per ml/min of inflow into the left circumflex coronary artery. Eleven dogs served as controls, whereas six dogs received NOE (74 µg/kg IV over 15 min before coronary microembolization, followed by 2.4 µg/kg/min for 8 hours).
Results: In both, controls and dogs receiving NOE, TNF-α content was increased in the microembolized posterior wall (controls: 2039 ± 1122 (mean± SD), NOE: 1510 ± 457 U/g wet weight) over that in the anterior wall (controls: 1070 ± 543, NOE: 973 ± 435 U/g wet weight). The sphingosine content was increased in the posterior wall in controls (406 ± 147 posterior vs. 244 ± 67 pmol/g wet weight anterior wall). While NOE did not change the sphingosine content in the anterior wall it completely prevented the increase in the posterior wall (241 ± 61 posterior vs. 200 ± 52 pmol/g wet weight anterior wall). Systemic hemodynamics and anterior systolic wall thickening remained unchanged for 8 hours after microembolization. Posterior systolic wall thickening in controls decreased progressively (20.6 ± 4.9 % at baseline to 4.1 ± 3.7 % at 8 hours after microembolization). In contrast, NOE prevented such decrease in contractile function (19.5 ± 5.7 % at baseline vs. 16.4 ± 6.3 % at 8 hours after coronary microembolization).
Conclusion: Sphingosine acts downstream of TNF-α and is causally involved in the coronary microembolization-induced progressive contractile dysfunction.

11:15 a.m.

886-4 **Antibodies to Human Heat Shock Protein 60 Predict Risk of Myocardial Infarction or Death in Women**

Jianhui Zhu, Joseph B. Muhlestein, Javier F. Nieto, Amy Wasserman, Benjamin D. Horne, Jeffrey L. Anderson, Stephen E. Epstein, *Washington Hospital Center, Washington, Dist. of Columbia, LDS Hospital, Salt Lake City, Utah.*

Background: We previously demonstrated that antibodies to human heat shock protein (HSP) 60 are associated with both the presence and severity of coronary artery disease (CAD). In the present prospective study, we examined the relation of human HSP60 antibodies to risk of myocardial infarction (MI) or death among patients with significant CAD by angiography. Methods: Blood samples from 880 patients (77% men, mean age 65 years)were tested for HSP60 IgG antibodies (ELISA). Mean follow-up was 3 years.